UNITED STATES DISTRICT COURT
DISTRICT OF NEW HAMPSHIRE

LISA D. CARPENTER
and JEFFREY D. CARPENTER

Plaintiff,

v.

ELI LILLY AND COMPANY, an Indiana corporation,

Defendant.

Case No. 1:14-cv-00540-AJ

DEFENDANT LILLY'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION FOR JUDGMENT ON THE PLEADINGS UNDER FED. R. CIV. P. 12(C)

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Cases **Page(s)**

Statutes and Rules

Regulations and Other Authorities

MEMORANDUM OF POINTS AND AUTHORITIES

INTRODUCTION

Plaintiffs bring state-law claims against Lilly in two categories: (i) they allege that the prescribing information for Cymbalta approved by the federal Food and Drug Administration ("FDA") inadequately warns against the risk of adverse symptoms that can accompany discontinuing Cymbalta, and (ii) they allege that Lilly's FDA-approved design for Cymbalta is defective. *See* Compl. (Dkt. No. 1) (Dec. 3, 2014) ¶ 1. The essence of Plaintiffs' warning claim is that Lilly should have included information in Cymbalta's FDA-approved prescribing information about the absolute rate of all adverse events seen at discontinuation in certain pre-approval clinical trials—information duly provided to the FDA but which the FDA did not include in Cymbalta's approved labeling. The essence of Plaintiffs' design-defect claim is that Lilly should have sold Cymbalta in lower dosages than approved by the FDA or in a delivery form (like a scored tablet) that would permit patients to cut pills in half to reduce the dosages.

As governing First Circuit and Supreme Court precedent make clear, both claims here are preempted by the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 et seq. For both the warning claim and design-defect claim, Plaintiffs' Complaint taken as true would impermissibly obligate Lilly to alter its FDA-approved warnings and design when the governing regulatory structure would prohibit such unilateral action in this situation. The First Circuit's recent decision in *In re Celexa* confirms that Plaintiffs' state-law claims must yield to competing federal-law duties and thus fail as a matter of law. *See In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 40-43 (1st Cir. 2015); *see also Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2477-78 (2013); *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2580-81 (2011). In harmony with this Circuit and the Supreme Court's binding authority, and in a straightforward

application of what is now hornbook preemption doctrine, this Court should grant Lilly's motion for judgment on the pleadings. *See* Fed. R. Civ. P. 12(c).

First, Plaintiffs' state-law failure-to-warn claims are preempted because they seek to require Lilly to unilaterally change its FDA-approved label for Cymbalta to include information that was already fully in the possession of the FDA when it approved Cymbalta and its labeling. Plaintiffs allege that the label inadequately conveys the risks of discontinuing Cymbalta, and that the label's inadequate discontinuation warning injured Plaintiffs. *See* Compl. ¶¶ 1, 37-43, 53-103. "[A]s the complaint reads, [Lilly] would need to change [Cymbalta's] label in order to avoid liability under state law." *See In re Celexa*, 779 F.3d at 40. At the same time, however, the FDCA prohibits manufacturers from unilaterally changing labels that the FDA has approved, unless the change fits within the category of changes that a manufacturer can make independently through the FDA's Changes Being Effected ("CBE") provision. *See id.* at 38. This narrow exception permits a manufacturer to change a label without FDA approval *only if* the change reflects "newly acquired information." *See id.* Yet, according to their own allegations on the face of the Complaint, Plaintiffs seek to have Lilly change its discontinuation warning to reflect information and data (on the frequency, severity, and duration of discontinuation symptoms) that Lilly presented to the FDA and that the FDA fully considered *before* the medicine and its labeling were ever approved. *See, e.g.*, Compl. ¶¶ 16, 18, 21, 22, 71, 82. By Plaintiffs' own allegations, then, Plaintiffs seek to have Lilly change its discontinuation warning based on information that by definition is not "newly acquired." The CBE mechanism, in turn, is unavailable to Lilly, meaning that "[Lilly] could not independently change its label to read as [Plaintiffs] say it should have read in order to comply with [state] law." *See In re Celexa*, 779 F.3d at 43. Plaintiffs' failure-to-warn claims must therefore yield to federal law.

Second, Plaintiffs' state-law design-defect claims are preempted because they seek to unilaterally require Lilly to alter its design for Cymbalta. Plaintiffs allege that, instead of designing, manufacturing, and distributing Cymbalta in its only FDA-approved forms (20-, 30-, or 60-milligram capsules), Lilly should have designed and produced the medicine in capsules containing smaller doses or in a different dosage form entirely, such as a scored tablet or a liquid. Compl. ¶¶ 1, 19, 24, 48-49. Federal law, however, affords Lilly *no* way to implement Plaintiffs' proposed alternative design without the FDA's approval. Once the FDA approves the new-drug application for a particular medicine, the manufacturer is absolutely prohibited from unilaterally making any "changes in the qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application." 21 C.F.R. § 314.70(b)(2)(i). Plaintiffs' design-defect claims, if taken as true, would make it impossible for Lilly to comply with both state and federal requirements. Federal law thus preempts these claims, as well.

BACKGROUND

I. The FDA Approval Process

The FDCA requires manufacturers to gain approval from the FDA before marketing any medicine in interstate commerce. *Bartlett*, 133 S. Ct. at 2470 (citing 21 U.S.C. § 355(a)). A manufacturer may secure FDA approval only by submitting a new-drug application ("NDA"), for a new drug, or an supplemental new-drug application ("sNDA"), for a new treatment. *In re Celexa* (citing 21 C.F.R. § 314.1 et seq.). The NDA is a voluminous compilation of materials including full reports of all clinical investigations, relevant nonclinical studies, the manufacturer's proposed labeling, a full description of the medicine's "composition, manufacture, and specification[s]" (including its dosage form and strength), a discussion of why

the medicine's benefits exceed its risks for the proposed indications, and any other data relevant to evaluating the medicine's safety and effectiveness. *Bartlett*, 133 S. Ct. at 2470; 21 U.S.C. § 355(b)(1); 21 C.F.R. §§ 314.50(c), (d). "The process of submitting an NDA is both onerous and lengthy," involving back-and-forth correspondence, follow-ups, and supplementary submissions. *Bartlett*, 133 S. Ct. at 2471. The FDA may approve an NDA only if it determines that the drug in question is "safe for use" and that, "based on a fair evaluation of all material facts," the proposed label is not "false or misleading in any particular." *In re Celexa*, 779 F.3d at 36 (citing 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)). The sNDA, meanwhile, is subject to the same requirements. *Id.* (citing 21 C.F.R. 314.1 et seq.).

The "default rule" is that a manufacturer may not change its FDA-approved label without re-securing the FDA's approval. *Id.* (citing 21 C.F.R. § 314.70(b)(2)(v)(A)). The sole exception to this rule is known as the Changes Being Effected ("CBE") procedure, through which a manufacturer may make certain types of changes to the label without prior FDA approval. *Id.* (citing 21 C.F.R. §§ 314.70(c)(6)(iii)). To make a change under the CBE exception, the change must reflect "newly acquired information." *Id.* at 37 (citing 21 C.F.R. § 314.70(c)(6)(iii)). The FDA itself has cautioned that the CBE procedure is "narrow" and a "limited exception to the general requirement of prior FDA approval for a labeling change." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, & Med. Devices, 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008).

Once the FDA approves an NDA, the manufacturer is also prohibited from unilaterally making any "changes in the qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application." 21 C.F.R. § 314.70(b)(2)(i). A manufacturer may not utilize the CBE mechanism or any other procedural

exception to unilaterally modify a medicine's design. *See id.*; *Bartlett*, 133 S. Ct. at 2471.

II. Cymbalta's Label and Design

In 2004, the FDA approved Cymbalta, a serotonin norepinephrine reuptake inhibitor (SNRI), for treatment of major depressive disorder. *See* Compl. ¶ 12; *see also* Declaration of Michael X. Imbroscio ("Imbroscio Decl."), Ex. A (Cymbalta Launch Label, Aug. 2004).[1] The FDA later approved new indications for, among other indications, generalized anxiety disorder, in 2007, and fibromyalgia, in 2008. *See* Compl. ¶ 12. From 2004 onward, the FDA has approved various versions of the Cymbalta label, including iterations that were approved in March 2011 and September 2011. *See id.* ¶ 16 (referencing label that was operative in 2004); *id.* ¶ 20 (referencing label that was operative in 2012); *id.* ¶¶ 31-33 (alleging that Plaintiff was prescribed Cymbalta in June 2011 and weaned off it in January 2012); *see also* Imbroscio Decl., Ex. B (Cymbalta Label, Mar. 2011, which was the operative label through June 2011);[2] Imbroscio Decl., Ex. C (Cymbalta Label, Sept. 2011, which was the operative label through January 2012).[3]

Since Cymbalta's launch, the FDA-approved label has consistently showcased a three-paragraph warning describing the potential for discontinuation symptoms. That warning has consistently conveyed: (i) detailed information on the specific discontinuation-related adverse events seen in the Cymbalta clinical trials at a statistically significantly higher rate than placebo *and* above a certain minimal threshold frequency (1% or 2%, depending on the label); (ii) detailed information on discontinuation-related adverse events observed across the SNRI and

[1] *See* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21427lbl.pdf; *see also* FDA, Drug Approval Package for Cymbalta (Aug. 2004), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021427_s000_Cymbalta.cfm.
[2] *See* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021427s036lbl.pdf.
[3] *See* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021427Orig1s039.pdf.

selective serotonin reuptake inhibitor (or SSRI) class of antidepressants; and (iii) guidance on tapering off the medicine to mitigate discontinuation symptoms:

> **Discontinuation of Treatment with Cymbalta**: Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.
>
> During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional instability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.
>
> Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see Dosage and Administration).

See Imbroscio Decl., Ex. A (Cymbalta Launch Label, Aug. 2004) at 6-7; *see also id.*, Ex. B (Cymbalta Label, Mar. 2011) ¶ 5.6 (listing individual discontinuation symptoms that occurred in clinical trials at a rate of 1%); *id.*, Ex .C (Cymbalta Label, Sept. 2011) ¶ 5.7 (same). The latter two paragraphs appear in labeling for all SSRIs and SNRIs at the FDA's discretion, and one federal court has already determined this labeling to be legally adequate. *McDowell v. Eli Lilly & Co.*, — F. Supp. 3d —, 2014 WL 5801604, at *11, *15 (S.D.N.Y. Nov. 7, 2014) (holding that Cymbalta's discontinuation warning is adequate as a matter of law because it is "accurate, clear, consistent on its face" and "portrays with sufficient intensity the risk involved in taking the drug" (citation and internal quotation marks omitted)), *mot. recons. denied*, No. 1:13-cv-03786-RWS (S.D.N.Y. Feb. 26, 2015). The medical and psychiatric community has long recognized that discontinuation symptoms may accompany SSRI/SNRI treatment. *See McDowell*, 2014 WL

5801604, at *3 (citing American Psychiatric Practice Guidelines).

Apart from Cymbalta's labeling, the FDA has also approved Cymbalta's particular design. Since Cymbalta entered the market, the FDA has approved Cymbalta for manufacture and distribution only in 20-, 30- or 60-milligram capsules. *See* Compl. ¶¶ 1, 19, 24, 48. As the Cymbalta label has described from initial approval, "Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach." *See* Imbroscio Decl., Ex. A (Cymbalta Launch Label, Aug. 2004) at 1. The labeling specifically instructs physicians to tell their patients not to open or otherwise tamper with the capsule: "Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating." *Id.* at 7.

III. Plaintiffs' Complaint

Plaintiffs are Lisa D. Carpenter, the principal plaintiff, and Jeffrey D. Carpenter, the consortium plaintiff. Compl. ¶ 2, 30, 35. Plaintiffs allege that Ms. Carpenter was prescribed Cymbalta in June 2011, elected to wean off Cymbalta in January 2012, and thereafter experienced discontinuation symptoms. *Id.* ¶ 31-33. Although Plaintiffs bring seven common-law causes of action against Lilly concerning Cymbalta's labeling and design, their Complaint boils down to two overarching theories. *Id.* ¶ 1. First, Plaintiffs claim that Lilly's FDA-approved label for Cymbalta inadequately warned about the frequency, severity, and duration of adverse symptoms that can accompany discontinuing treatment with Cymbalta. *E.g., id.* ¶¶ 1, 16, 18, 20-22, 71, 82. Plaintiffs urge that, while a subset of Lilly's clinical studies conducted to secure FDA approval of Cymbalta showed that about 44% of patients experienced

discontinuation symptoms (compared with 23% of placebo patients), Lilly omitted this information from Cymbalta's label. *Id.* According to Plaintiffs, the Cymbalta label should have included the 44% data. *Id.* Second, Plaintiffs claim that Lilly's distribution of Cymbalta in its only FDA-approved form—20-, 30-, and 60-milligram capsules—amplified the risk of discontinuation symptoms and injured Plaintiffs. *Id.* ¶¶ 1, 19, 24, 48. Plaintiffs urge that Lilly should have made Cymbalta available either in different dosages or in a tablet form that could have been cut to administer even lower dosages. *Id.*

LEGAL STANDARD

A motion for judgment on the pleadings may be brought at any time after the pleadings are closed, so long as the motion is filed early enough not to delay trial. Fed. R. Civ. P. 12(c). The court must "accept all of the nonmoving party's well-pleaded factual averments as true and draw all reasonable inferences in her favor." *Feliciano v. State of R.I.*, 160 F.3d 780, 788 (1st Cir. 1998). But this standard is far from "meaningless." *Scarano v. Cmty. Corr. Corp.*, 2001 WL 873059, at *1 (D.N.H. July 19, 2001) (emphasizing that a court need not accept every allegation). "To survive a motion for judgment on the pleadings, the 'complaint must establish a plausible entitlement to relief.'" *Lacaillade v. Loignon Champ-Carr, Inc.*, 2010 WL 2902251, at *2 (D.N.H. July 22, 2010) (citation omitted). That is, the complaint must plead facts that "raise a right to relief above the speculative level" and that contain "enough meat to support a reasonable expectation that an actionable claim may exist." *Id.* (citations and internal quotation marks omitted). "The court may supplement the facts contained in the pleadings by considering documents fairly incorporated therein and facts susceptible to judicial notice." *R.G. Fin. Corp. v. Vergara-Nunez*, 446 F.3d 178, 182 (1st Cir. 2006); *accord Curran v. Cousins*, 509 F.3d 36, 44 (1st Cir. 2007) (confirming that a court may venture beyond the pleadings to consider documents

such as those "central to plaintiffs' claim" or "sufficiently referred to in the complaint" (citation and internal quotation marks omitted)); *Jardin De Las Catalinas Ltd. P'ship v. Joyner*, 766 F.3d 127, 132 (1st Cir. 2014); *Carey v. Olson*, 2006 WL 1081191, at *1 (D.N.H. Apr. 21, 2006).

Preemption is a suitable basis for a Rule 12(c) judgment. *See, e.g.*, *Zipperer v. Raytheon Co.*, 493 F.3d 50, 53-55 (1st Cir. 2007). Under the Constitution's Supremacy Clause, the laws and treaties of the United States "shall be the supreme Law of the Land . . . , any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Therefore, state laws that conflict with federal law are "without effect." *Bartlett*, 133 S. Ct. at 2473 (citation and internal quotation marks omitted). Even in the absence of an express preemption provision, a state law is impliedly preempted where it is "impossible for a private party to comply with both state and federal requirements." *Id.* (citation and internal quotation marks omitted); *see also In re Celexa*, 779 F.3d at 40 (adding that conflict preemption also applies "where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress") (citation and internal quotation marks omitted).

ARGUMENT

I. The Governing Legal Framework: *In re Celexa*

This case is governed by the First Circuit's recent decision of *In re Celexa*, which itself synthesized the recent trilogy of Supreme Court decisions addressing whether federal law preempts state-law claims brought against manufacturers of prescription medicines. *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 40-43 (1st Cir. 2015); *Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2477-78 (2013); *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2580-81 (2011); *Wyeth v. Levine*, 555 U.S. 555, 569-70 (2009).

In *In re Celexa*, the plaintiffs brought state-law claims against Forest, the manufacturer of

Lexapro, alleging that Lexapro's FDA-approved label was "misleading and inadequate" as to the medicine's efficacy. 779 F.3d at 35, 38. The First Circuit ruled that the FDCA preempted the plaintiffs' claims because it was impossible for Forest to comply with the state-law obligations imposed by the plaintiffs' claims, on the one hand, and the federal-law obligations imposed by the FDCA, on the other. *Id.* at 40-43.

As an initial matter, the court noted that the plaintiffs' claims sought to impose state-law requirements on Forest: Accepting the plaintiffs' complaint as true, Forest would need to revise its Lexapro label in order to avoid liability under state law. *Id.* at 40. The court then observed that a manufacturer may not change an FDA-approved label independently—that is, without the FDA's approval—unless the manufacturer is changing the label based on "newly acquired information" through the CBE exception. *Id.* at 38. Relying on the Supreme Court precedents of *Wyeth*, *PLIVA*, and *Bartlett*, the court proceeded to hold that a "necessary step in defeating Forest's preemption defense is to establish that the complaint alleges a labeling deficiency that Forest could have corrected using the CBE regulation." *Id.* at 41. Otherwise, Forest's state-law duty to alter the label would conflict with its federal-law duty to maintain the label—which would trigger preemption of the state-law claims. *Id.* at 40-43.

Notably, the First Circuit's reasoning was rooted in Supreme Court precedent. *Id.* at 40-41. In distinguishing between "changes that can be independently made through the CBE regulation" and "changes that require prior FDA approval," the First Circuit made clear that it was merely tracing the sensible line that the Supreme Court itself had drawn between these two categories. *Id.* at 41.

In *Wyeth v. Levine*, 555 U.S. 555 (2009), for example, the Supreme Court spared the plaintiff's state-law failure-to-warn claims from preemption—but only because the plaintiff

wanted the manufacturer's brand-name label to reflect "accumulating data" that the FDA had *not* considered. *Id.* at 569-70. The Court reasoned that since such information was "newly acquired," the manufacturer could have, but did not, utilize the CBE mechanism to independently modify the label. *Id.* Later, in *PLIVA*, the Court held that the plaintiffs' state-law failure-to-warn claims against generic manufacturers were preempted because, under federal law, a generic manufacturer is not only prohibited from deviating from the brand-name label, but is also categorically barred from the CBE procedure. 131 S. Ct. at 2575-79. Federal law afforded the generic manufacturers no way to independently accommodate the plaintiffs' state-law demands; preemption was warranted. *Id.*; *accord Bartlett*, 133 S. Ct. at 2470-71, 2476 (same with respect to design-defect claims that turned on the label's adequacy).

As the First Circuit observed, *Wyeth*, *PLIVA*, and *Bartlett* taken together stand for the principle that the touchstone for preemption of a plaintiff's state-law claim against a pharmaceutical manufacturer is the availability of the CBE procedure: The plaintiff's claim avoids preemption *only if* the manufacturer may validly and *independently*—that is, consistent with federal law, and without the FDA's assistance—take the action that the plaintiff alleges is required under state law. *See In re Celexa*, 779 F.3d at 41; *see also id.* ("The [Supreme] Court thus limited *Wyeth* to situations in which the drug manufacturer can, of its own volition, strengthen its label in compliance with its state tort duty.") (citation, internal quotation marks, and alterations omitted).

For the First Circuit in *In re Celexa*, then, the dispositive question for preemption was "whether the CBE regulation allows a brand name manufacturer to make the particular type of [labeling] change that [the] plaintiffs say Forest needed to have made to avoid liability under [state] law." *Id.* Turning to that issue, the court determined that the plaintiffs were not seeking a

labeling change based on "newly acquired information." *Id.* The plaintiffs' complaint had failed to demonstrate that the information they wanted in the label was unknown to the FDA before it approved the label. *Id.* at 42-43; *see also id.* at 42 ("[The plaintiffs] do not argue, however, that the FDA was unaware of this fact."); *id.* at 43 ("[The plaintiffs] make no claim, however, that this information was unknown to the FDA prior to label approval."). Consequently, the plaintiffs were "stymied": "Forest could not independently change its label to read as [the] plaintiffs say it should have read in order to comply with [state] law." *Id.* at 43.

II. Federal Law Preempts Plaintiffs' State-Law Failure-to-Warn Claims.

The same result is dictated here. Taken as true, Plaintiffs' failure-to-warn claims would obligate Lilly to revise its Cymbalta label in order to avoid liability under state law. But the FDCA prohibits Lilly from independently changing the Cymbalta label under federal law to include information that was already fully in the FDA's possession prior to the approval of the medicine. In these circumstances, Lilly cannot use the CBE procedure to include this information, and thus it would be impossible for Lilly to comply with both state and federal requirements. Because Lilly's supposed state obligations must yield to its federal obligations, Plaintiffs' failure-to-warn claims are self-abrogating and must be dismissed.

A. Plaintiffs' State-Law Claims, If Taken as True, Would Require Lilly to Change Its Cymbalta Label.

As a threshold matter, there is no dispute that Plaintiffs' failure-to-warn claims seek to impose state-law requirements on Lilly. *See Bartlett*, 133 S. Ct. at 2479 (foreclosing any argument to the contrary). Here, as in *In re Celexa*, "Plaintiffs' complaint seeks to impose liability on [Lilly] because of what [Cymbalta's] FDA-approved label states or fails to state. In other words, as the complaint reads, [Lilly] would need to change [Cymbalta's] label in order to avoid liability under state law." 779 F.3d at 40.

B. Lilly's Federal-Law Duties Preclude It From Independently Changing the Label.

Although Plaintiffs' state-law claims would require Lilly to change its label to avoid state common-law liability, federal law forbids Lilly from taking unilateral action in these circumstances. The "default rule" is that Lilly may not change its FDA-approved label without re-securing the FDA's approval. *See In re Celexa*, 779 F.3d at 37 (citing 21 C.F.R. § 314.70(b)(2)(v)(A)). The sole exception is the narrow pathway of the CBE provision, through which Lilly may change the label without prior FDA approval, but *only if* the change reflects "newly acquired information." *Id.*; 21 C.F.R. §§ 314.70(c), (c)(6)(iii). Under the controlling authority of *In re Celexa*, "a *necessary* step in defeating [Lilly's] preemption defense is to establish that the complaint alleges a labeling deficiency that [Lilly] could have corrected using the CBE regulation," which is "*only* available to make changes" based on "newly acquired information." *See In re Celexa*, at 41-42 (emphasis added).

"Newly acquired information" is defined as "data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveals risks of a different type or greater severity or frequency than previously included in submissions to the FDA." *Id*. at 42 (quoting 21 C.F.R. § 314.3(b)); *see also* Supplemental Applications, 73 Fed. Reg. at 2849 (cautioning that the CBE procedure is "narrow" and "limited").

According to their Complaint, however, Plaintiffs' failure-to-warn theory is that the FDA-approved label neglects to include information about Cymbalta's discontinuation risks from Lilly's own *pre-approval clinical trials*. *See* Compl. ¶¶ 1, 20-22, 25, 40, 56, 71, 80, 82,

93. But there is no dispute that Lilly provided the very same pre-approval clinical data concerning Cymbalta's discontinuation risks to the FDA before Cymbalta's launch. Because Plaintiffs seek to change the label to reflect the very same data that Lilly provided to the FDA before the FDA approved the label, Plaintiffs' desired labeling change is not based on "newly acquired information." After all, the FDA was indisputably aware of that data when it approved the Cymbalta label.

Indeed, the critical allegation that animates Plaintiffs' failure-to-warn claims is that the FDA-approved label is missing certain specific findings from Lilly's clinical trials—namely, that around 44% of a subset of the clinical-trial patients experienced some type of discontinuation symptom. *Id.* ¶¶ 20-22, 71, 82. As Plaintiffs' Complaint reads, this particular datum is the central focus of the entire litigation. *See id.* And yet Plaintiffs cannot (and do not) contest that Lilly provided this datum to the FDA before the FDA approved the label. The FDA was well aware of it; there is no sense in which it can be deemed "newly acquired."

In effect, the gravamen of Plaintiffs' failure-to-warn case is that, while the FDA-approved label lists only those discontinuation symptoms that occurred in the clinical trials at a significantly higher rate for Cymbalta compared to placebo and above a minimal threshold rate (initially 2% and then expanded to 1%), Lilly should have described the data in a different way. *Id.* In Plaintiffs' view, Lilly should have described the frequency of all adverse events regardless of whether the adverse events occurred at a higher rate for Cymbalta versus placebo and regardless of whether the adverse events were reasonably connected with the medicine. *Id.* In their view, Cymbalta's labeling should have stated that "between 44.3% and 50% of Cymbalta patients suffered from discontinuation side effects" in a subset of its clinical trials, and that "between 9.7% and 17.2% of Cymbalta users suffered severe withdrawal symptoms." *Id.* ¶¶ 20-

22, 71, 82. Plaintiffs derive this data from Lilly's own publication of its pre-approval clinical studies in a 2005 article of the Journal of Affective Disorders, titled *Symptoms Following Abrupt Discontinuation of Duloxetine Treatment in Patients with Major Depressive Disorder*, by David G. Perahia and others ("2005 JAD Article"). *Id.* ¶¶ 21, 71, 82; *see also* Imbroscio Decl., Ex. D (2005 JAD Article). According to Plaintiffs, despite Lilly's "knowledge" of the frequency, severity, and duration of Cymbalta's discontinuation symptoms from its clinical trials, by presenting the data in the manner approved by the FDA, Lilly "omitted this critical information from its label" and "misleadingly" obscured the risks by stating that discontinuation symptoms occur at a rate of 1% rather than 44%. *E.g.*, *id.* ¶¶ 21, 71, 82.[4]

Yet, even accepting Plaintiffs' mischaracterization of the Cymbalta labeling, there is no dispute that all the pre-approval clinical trial data that supported the initial Cymbalta labeling (and that made up the content of the 2005 JAD Article) were already long-provided to FDA as part of the approval process for Cymbalta. Plaintiffs make no allegation to the contrary—nor could they, in light of the extensive requirements for obtaining a medicine's approval, including the submission of all clinical data and clinical reports. *See* 21 U.S.C. § 355(b)(1) (mandating that applicants submit clinical reports); 21 C.F.R. § 314.50(d)(5) (mandating that applicants submit clinical data). Indeed, not only did Lilly submit to the FDA all the individual clinical trials that constituted the dataset for the 2005 JAD Article, but Lilly also submitted to the FDA a pooled analysis of the trials that included the precise 44% figure upon which Plaintiffs hinge their case. *See* Imbroscio Decl., Ex. E (Lilly's NDA Submission to FDA, Mar. 24, 2003) at 135

[4] In *McDowell*, Judge Sweet firmly rejected Plaintiffs' mischaracterization of Cymbalta's labeling. *McDowell*, 2014 WL 5801604, at *12-14 (recognizing that the label's plain language does *not* imply that the risk of experiencing discontinuation symptoms is "1%," but rather lists each individual discontinuation symptom that occurred at or above a rate of 1% in clinical studies).

(conveying the percentages from Lilly's clinical trials that are central to Plaintiffs' allegations, including "44.3%"). Before approving the Cymbalta launch label in August 2004, and before approving each updated label thereafter, the FDA reviewed the information and data that Lilly placed before it, including information and data about Cymbalta's discontinuation risks, and determined that Lilly's Cymbalta label was not "false or misleading in any particular." *See* 21 U.S.C. § 355(d)(7); 21 C.F.R. § 314.125(b)(6); *see also McDowell*, 2014 WL 5801604, at *6 ("Lilly conducted clinical trials . . . . These results were published in the 2005 JAD Article. . . . In addition, as required by regulation, Eli Lilly also provided the study to the FDA.") (citing FDA, *Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* (1996), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf, at 15-16).[5]

At bottom, Plaintiffs' central complaint is that they do not like the way the FDA and Lilly have chosen to describe the Cymbalta clinical trial data. But disagreement in the manner of presentation goes to the heart of why federal preemption exists: The FDA could reasonably have decided not to include the total adverse event statistics because those numbers—the 44.3% on Cymbalta and the 23% on placebo—are not meaningful to the clinician and indisputably contain a wide array of adverse events that no one reasonably would associate with Cymbalta treatment, including reported events like "[p]regnancy," "[a]rthropod bite[s]" and "sting[s]," and "[f]ood poisoning." *See* Imbroscio Decl., Ex. E (Lilly's NDA Submission to FDA, Mar. 24, 2003) at 138-40. Instead, FDA and Lilly decided to feature those adverse events (i) that reasonably related to Cymbalta because of a statistically significantly higher reporting rate and (ii) that

[5] Lilly's FDA-approved labels, the 2005 JAD Article, and its submissions to the FDA are all susceptible to judicial notice and central to Plaintiffs' allegations. *See, e.g.*, Compl. ¶ 1, 16, 20-22, 82. This Court may properly consider these documents in adjudicating a Rule 12(c) motion for judgment on the pleadings. *See, e.g.*, *R.G. Fin.*, 446 F.3d at 182; *Curran* 509 F.3d at 44.

appeared at or above a de minimis threshold (first 2%, then 1%). *See* Imbroscio Decl., Ex. A (Cymbalta Launch Label, Aug. 2004) at 6-7 ("[T]he following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo . . . ."). As the *McDowell* court held, "This method of communicating information on individual symptoms appearing in clinical trials is consistent with the accepted practice of identifying such individual adverse events observed at or above a specified threshold and in accord with FDA regulations and guidance directing that the label 'list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database.'" *See McDowell*, 2014 WL 5801604, at *12 (citing 21 C.F.R. § 201.57(c)(7)); *see also id.* at *14 ("Using a numerical threshold for the inclusion of adverse events in a label is an appropriate, standard methodology for identifying adverse events arising with sufficient frequency to warrant inclusion in the product label.").

Just as in *In re Celexa*, "the change [Plaintiffs] seek in the label is indeed based on information . . . that was plainly known to the FDA prior to approving the label." *See In re Celexa*, 779 F.3d at 43. The information that Plaintiffs demand that the label reflect does not "reveal risks of a different type or greater severity or frequency than previously included in submissions to the FDA." *See* 21 C.F.R. § 314.3(b). Because the data from the pre-approval trials upon which Plaintiffs base their claim cannot by law be deemed "newly acquired," Lilly may not utilize the CBE procedure to reconfigure the warning to Plaintiffs' liking. As a result, Plaintiffs' failure-to-warn claims are preempted. *See In re Celexa*, 779 F.3d at 41-43.

C. Because Lilly Cannot Independently Do Under Federal Law What Plaintiffs' State-Law Failure-to-Warn Claims Would Require, They Are Preempted.

As the Supreme Court observed in *PLIVA*: "The question for impossibility is whether the private party could *independently* do under federal law what state law requires of it." 131 S. Ct.

at 2579 (citing *Wyeth*, 555 U.S. at 573) (emphasis added). Because Lilly cannot utilize the CBE mechanism in these circumstances to change Cymbalta's label without the FDA's approval, Lilly cannot "independently change its label to read as [Plaintiffs] say it should [] read in order to comply with [state] law." *See In re Celexa*, 779 F.3d at 43. As a matter of settled preemption doctrine, therefore, Plaintiffs' claims are preempted and must be dismissed. *See id.*

It is no matter that Lilly *could* have asked the FDA to implement the labeling revision that Plaintiffs urge. Under the principles of impossibility preemption, as crafted by the Supreme Court and endorsed by the First Circuit, "the possibility that the FDA would [] agree[] to require such a change [does] not preclude the court from concluding that compliance with both state and federal [labeling] requirements [is] impossible." *In re Celexa*, 779 F.3d at 41; *accord PLIVA*, 131 S. Ct. at 2579-81. In *PLIVA*, for example, the plaintiffs sued generic manufacturers, alleging that the generic label for metoclopramide inadequately warned about the risk of tardive dyskinesia, a neurological disorder. 131 S. Ct. at 2575-78. According to federal law, a generic label must mirror the brand-name label; a generic manufacturer cannot revise a label without the FDA's approval; and the CBE procedure is not available to a generic manufacturer. 131 S. Ct. at 2575-78. As a result, the generic manufacturers could not independently incorporate the plaintiffs' desired labeling modifications. *Id.* But the plaintiffs were undeterred, pinning their argument against preemption on the notion that, "if the Manufacturers had asked the FDA for help in changing the corresponding brand-name label, they might eventually have been able to accomplish under federal law what state law requires." *Id.* at 2578. The Supreme Court, however, declined plaintiffs' invitation to deflate the doctrine of impossibility preemption. *Id.* Although one can "imagine that a third party of the Federal Government *might* do something that makes it lawful for a private party to accomplish under federal law what state law requires of it,"

the Supremacy Clause does not "contemplate[] that sort of contingent supremacy." *Id.* at 2579-80. The Court held that "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for preemption purposes." *Id.* at 2580-81; *see also id.* at 2580 ("When the 'ordinary meaning' of federal law blocks a private party from independently accomplishing what state law requires, that party has established pre-emption.").

Here, too, the FDCA blocks Lilly from independently changing its label for Cymbalta—whether by threading the needle of the CBE exception or otherwise. *In re Celexa*, 779 F.3d at 41-43. Accordingly, Lilly has established preemption. *See id.* The possibility that Lilly could have requested the FDA's assistance in conforming the label to Plaintiffs' wishes does not save Plaintiffs' claims from dismissal. *See PLIVA*, 131 S. Ct. at 2580; *In re Celexa*, 779 F.3d at 41.

Furthermore, as the First Circuit reasoned in *In re Celexa*, it makes "pragmatic sense" to preempt state-law claims that would compel a manufacturer to independently change a label in defiance of federal law. *See* 779 F.3d at 41. "By hinging preemption on the availability of [the CBE] procedure in a particular case," the Supreme Court's preemption jurisprudence "lets the FDA be the exclusive judge of safety and efficacy based on information available at the commencement of marketing," and "effectively reserves the launch of new drugs to the expertise of the FDA," but then "preserves a wide scope for the states in requiring manufacturers to respond to information not considered by the FDA." *See id.* By extinguishing state-law claims that would otherwise compel Lilly to revise the Cymbalta label based on information that the FDA had considered when it approved the label but chose to present in a different manner, the principles of preemption ensure that state law will not disrupt the FDA's careful federal

balancing and considered federal judgment. *See In re Celexa*, 779 F.3d at 41.

III. Federal Law Preempts Plaintiffs' State-Law Design-Defect Claims.

Plaintiffs' state-law design-defect claims similarly fail as a matter of law. Federal law prohibits Lilly from unilaterally implementing the alternative design that Plaintiffs' state-law claims seek. Because it is impossible for Lilly to comply with its state and federal duties, Plaintiffs' design-defect claims are likewise preempted.

A. Plaintiffs' State-Law Claims, If Taken as True, Would Require Lilly to Alter Its Cymbalta Design.

In support of their design-defect claims, Plaintiffs allege that the capsules for Cymbalta are defective because: (i) Lilly does not produce them in doses smaller than 20 milligrams; and (ii) the capsules cannot be split or opened to permit a patient to fashion a smaller dose from a single capsule. Compl. ¶¶ 1, 19, 24, 48-49. According to Plaintiffs, Cymbalta's allegedly deficient design precludes a patient from taking a dose smaller than 20 milligrams, which hinders the patient's ability to gradually taper off the medicine, and which in turn heightens discontinuation risks. *Id.* Ultimately, the essence of Plaintiffs' design-defect claims is that, instead of designing, manufacturing, and distributing Cymbalta in its only FDA-approved form (20-, 30-, or 60-milligram capsules), Lilly should have designed and produced the medicine in capsules containing smaller doses, or in "scored tablets that can be halved and quartered with relative ease," or in "liquid form which can be measured and dispensed in small increments." *Id.* As Plaintiffs' Complaint reads, Lilly must alter its design for Cymbalta if it is to avoid liability under state law. *See Bartlett*, 133 S. Ct. at 2479.

B. Lilly's Federal-Law Duties Preclude It From Independently Changing the Design.

Lilly may not unilaterally implement Plaintiffs' proposed alternative design without violating federal law. Once the FDA approves the NDA for a particular medicine, the

manufacturer is prohibited from unilaterally making any "changes in the qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application." 21 C.F.R. § 314.70(b)(2)(i); *Bartlett*, 133 S. Ct. at 2471. Rather, the manufacturer may make any such changes only by submitting an sNDA and re-securing FDA approval through an onerous and lengthy review process. *See* 21 C.F.R. § 314.70(b)(3); *In re Celexa*, 779 F.3d at 36 (citing 21 C.F.R. 314.1 et seq.). Changes that require such pre-approval include qualitative or quantitative changes to a medicine's dosage form, such as a change in dose strength or a conversion from a capsule to a tablet or a liquid. *See* 21 C.F.R. § 314.70(b)(2)(i) (stating that changes in "qualitative or quantitative formulation" of "drug product" require pre-approval); 21 C.F.R. § 314.3 (defining "drug product" as "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance"); *see also* 21 U.S.C. § 356a(c)(2)(A) (stating that a change in "qualitative or quantitative formulation of the drug" is "major change[]" requiring pre-approval). In fact, regulatory guidance materials from the FDA suggest that changes such as those Plaintiffs have proposed might require the submission and approval of an entirely new NDA—as opposed to an sNDA.[6]

If a manufacturer circumvents this legally-mandated framework for medicinal design and unilaterally alters the composition of its medicine, it becomes subject to federal enforcement action. Indeed, a manufacturer that flouts this framework may be subject to criminal prosecution. *See* 21 U.S.C. §§ 331(d), 333(a) (imposing criminal sanctions for introducing unapproved drugs into interstate commerce).

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[6] *See* FDA, *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf (advising the applicant to submit its change-in-dosage form "as a separate original application").

In light of the comprehensive federal regulatory scheme for medicinal composition, there is no dispute that Lilly could not unilaterally manufacture and distribute Cymbalta in a new dosage form or strength. Even if it were technically feasible, the alternative design that Plaintiffs claim is required under state law—that is, distribution in capsules containing smaller doses or in a tablet or liquid form—would at a minimum require the FDA's review and pre-approval.

C. Because Lilly Cannot Independently Do Under Federal Law What Plaintiffs' State-Law Design-Defect Claims Would Require, They Are Preempted.

Because Lilly could not unilaterally implement the alternative design that Plaintiffs claim is required under state law, federal law preempts Plaintiffs' design-defect claims. Plaintiffs' claims may not escape preemption based on the mere possibility that Lilly could have solicited the FDA's special assistance in altering Cymbalta's composition to suit Plaintiffs. The Supreme Court and the First Circuit have made clear that, where state law would require action that a pharmaceutical manufacturer could not take without the FDA's prior approval, or without the FDA's special assistance, impossibility preemption negates the state requirement. *See PLIVA*, 131 S. Ct. at 2580-81; *Bartlett*, 133 S. Ct. at 2476-77; *In re Celexa*, 779 F.3d at 41-43.

Bartlett is particularly instructive. There, the Supreme Court reasoned that any state law that requires alteration of a medicine's composition necessarily conflicts with federal law that prohibits a manufacturer from unilaterally altering the composition of its product. *See* 133 S. Ct. at 2478-79 ("[W]e hold that state-law design defect claims like New Hampshire's that place a duty on manufacturers to render a drug safer by either altering its composition or altering its labeling are in conflict with federal laws that prohibit manufacturers from unilaterally altering drug composition or labeling.").

To be sure, in the aftermath of *Wyeth*, *PLIVA*, and *Bartlett*, plaintiffs bringing design-defect claims against brand-name manufacturers have attempted to elude the Supreme Court's

authority by insisting that these decisions apply only to cases involving *generic* manufacturers. This false distinction is easily dispatched. ***First***, *PLIVA* and *Bartlett* were decided on the basis of a clear preemption rule that is not in any way limited to the generics context. *See PLIVA*, 131 S. Ct. at 2580-81 ("To decide these cases, it is enough to hold that when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for preemption purposes."); *Bartlett*, 133 S. Ct. at 2471, 2479 ("Once a drug—***whether generic or brand-name***—is approved, the manufacturer is prohibited from making any major changes to the qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application.") (emphasis added) (internal quotation marks omitted).

Second, although Plaintiffs might look to *Wyeth* to avoid preemption, *Wyeth*'s result was driven by the brand-name manufacturer's ability to use the CBE mechanism to modify its label to include newly available information—not by any intrinsically different set of duties between brand-name and generic manufacturers. In the design-defect context, it is indisputable that neither a brand nor a generic manufacturer may alter FDA-approved dosages and formulations. As the First Circuit emphasized in synthesizing the Supreme Court's preemption trilogy, "The [Supreme] Court thus limited *Wyeth* to situations in which the drug manufacturer can, of its own volition, strengthen its label in compliance with its state tort duty." *In re Celexa*, 779 F.3d at 41 (citation, internal quotation marks, and alterations omitted)).

Third, courts have routinely followed *PLIVA* and *Bartlett*'s logic to conclude that claims against brand-name manufacturers are preempted for the same reason that such claims against generic manufacturers are preempted: when it is impossible for *any* pharmaceutical

manufacturer—generic or brand-name—under the applicable federal regulatory framework to take certain actions (including alteration of the design of its product) without first seeking FDA approval. *See Yates v. Ortho-McNeil Pharm., Inc.*, — F. Supp. 3d —, 2015 WL 66423, at *5-7 (N.D. Ohio Jan. 5, 2015) (relying on *Bartlett* to conclude that design-defect claim against manufacturer of brand-name birth control patch was preempted: "Although Ms. Yates' attorneys assert that the preemption is applicable to only generic drugs, the language in *Bartlett* and *Amos* is not so restrictive."); *Booker v. Johnson & Johnson*, 54 F. Supp. 3d 868, 873-75 (N.D. Ohio 2014) (relying on *Bartlett* to conclude that design-defect claim against manufacturer of brand-name birth control patch was preempted: "[I]t was impossible for the Defendants to comply with both its state-law duty to alter the composition of the drug, and its federal-law duty not to alter an FDA-approved design. Accordingly, Plaintiff's design defect claim fails as a matter of law."); *Amos v. Biogen Idec Inc.*, 28 F. Supp. 3d 164, 169 (W.D.N.Y. 2014) (relying on *Bartlett* to conclude that design-defect claims against manufacturer of brand-name multiple sclerosis medicine were preempted: "[T]he [Supreme] Court held that because a drug manufacturer could not simultaneously comply with FDA requirements mandating the specific design of an approved drug and state-law requirements mandating that the design be altered, the state-law requirements were preempted by federal law."); *Thompson v. Allergan USA, Inc.*, 993 F. Supp. 2d 1007, 1013-14 (E.D. Mo. 2014) (relying on *PLIVA* and *Bartlett* to find state-law claims preempted where plaintiffs alleged that manufacturer of brand-name prescription eye medication should have distributed medicine in vials containing smaller quantities: "*Bartlett* extended the holding of [*PLIVA*] to cover not just failure-to-warn claims, but also those claims that would require a redesign of a drug.").

CONCLUSION

Under principles of impossibility preemption that now constitute blackletter law in this Circuit, federal law preempts both Plaintiffs' failure-to-warn and design-defect claims. Accordingly, the Court should grant Lilly's Rule 12(c) motion for judgment on the pleadings and dismiss Plaintiffs' Complaint with prejudice.

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Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Memorandum of Law in Support of Defendant Lilly's Motion for Judgment on the Pleadings Under Fed. R. Civ. P. 12(c) was sent this 22nd day of May, 2015, via ECF to Leslie C. Nixon, Esquire, and Robert B. Wisner, counsel of record.

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